

Aseptic Processing Contamination Case Studies and the Pharmaceutical Quality System

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ABSTRACT: This paper summarizes parenteral drug contamination case studies presented at industry conferences and a Food and Drug Administration advisory committee meeting in the period of 2000-2004. CGMP deficiencies associated with each contamination event are discussed. The key role of a well-functioning quality system in contamination prevention is emphasized.

Introduction

While many references (1–7) discuss principles of aseptic process control, fewer publications illustrate the practical impact of substandard production practices on a product purporting to be sterile. By examining case studies, the tangible consequences of a breakdown of one or more elements of current good manufacturing practice (CGMP) can be explored. (8,9)

Three prevalent themes are central to the vast number of aseptic processing contamination problems:

- poor personnel practice
- loss of environmental control
- flawed operational design

One or a combination of these CGMP deviations has led to contamination of aseptically processed products, including parenterals, ophthalmics, and aqueous inhalers (10, 11). While personnel practice or a loss of environmental control are normally named as the immediate source of a sterility problem, the investigation into root cause (12) frequently also concludes that changes in operational design are needed to implement a lasting solution.

Quality is built into a product produced by aseptic manufacture when sound process, equipment, and facility design is employed to minimize or eliminate potential contamination hazards. Modern design approaches include systematic evaluation of potential process vulnerabilities and holistic awareness of how daily dynamic operational factors can interact (13, 14). This process understanding should lead to dependable design choices. The new process is then supported

throughout the product lifecycle by a robust quality system that provides the infrastructure for continuous improvement (15) and consistent contamination prevention in accordance with 21 CFR 211.42 and 211.113 (16).

The Quality System

Figure 1 is a diagram of six basic elements of a pharmaceutical operation, based on the finished drug CGMP regulations (21 CFR 210 and 211). These interrelated elements are outlined in the Food and Drug Administration's (FDA's) Drug Manufacturing Inspections compliance program (17) and are known collectively as the *quality system* (18). As depicted by the diagram (19), a quality system provides the nucleus that drives the proper functioning of each of the five manufacturing systems. The quality system integrates all of these elements and its placement at the center is also meant to signify a sixth system of quality assurance (e.g., quality management, SOP review and approval, batch release). The case studies in this paper illustrate how drug product contamination stemmed from deficiencies in one or more system. This paper expands upon previously published contamination case studies (20) by emphasizing the single quality system element that appeared to be most deficient as the process drifted, generally undetected for a significant period, from its state of control.

Case Study 1: Aseptic Processing of a Sterile Active Pharmaceutical Ingredient (API)

Background

A sterile active pharmaceutical ingredient (API) manufacturer shipped numerous lots of an aseptically pro-

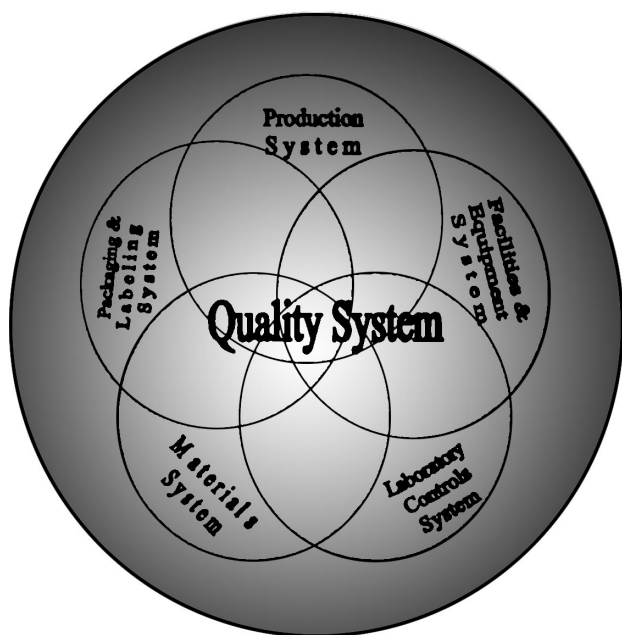


Figure 1

The Quality System

cessed drug to a finished dosage form customer. The lots were later found to lack assurance of sterility. Aseptic manufacture of this sterile API relied heavily on manual manipulations. A pronounced trend of sterility failures occurred at both the API site and at the customer's laboratory. It was determined that the contamination occurred during aseptic production of the API.

CGMP Issues

Although manufacturing practices at the finished dosage form site were found to be compliant, the FDA identified major CGMP issues at the API site. The design of the process did not assure adequate protection from microbial contamination, and personnel routinely performed many intensive manual manipulations that could imperil the exposed sterile product. However, the process simulation (i.e., media fill) program was not adequately representative of the actual manufacturing process. Examples of process simulation deficiencies included

- The firm used a microbiologically inhibitory material (very high pH) as the medium for the process simulation. The suitability of the culture medium was not evaluated (e.g., lack of data on inherent growth promotion capability of the me-

dium and effects of residual medium on membrane filter).

- During process simulations, the firm dried the media at 85–95 °C. This temperature contrasted with the 20–25 °C conditions used for the API process. The use of high temperatures for drying in the process simulation did not reflect the actual processing parameters. It might be expected that a significant number of vegetative microbial contaminants would be killed at the high, non-representative temperature.

Quality System Context

In this case, the *production system* was most deficient. In addition to aseptic process design deficiencies, the process simulation validation program was inadequate. Without a sufficiently sensitive process simulation program, there was a consequent loss of a media fill's basic benefits of promptly detecting and diagnosing an existing source of contamination.

In a strong quality system, it is essential that a sound scientific foundation (21) support reliable daily decision making. In particular, good science should pervade a pharmaceutical manufacturer's approaches to product development, process validation, standard operating procedures (SOPs) and investigations. Two of these, product development and process validation, involve studies intended to yield important information about a product or process. In the event of a poorly conceived study, conclusions based on assumptions may lead to erroneous process design decisions, with a consequent risk to product quality. A Compliance Policy Guide issued by FDA in March 2004 (22) stresses the importance of rational experimental design and continuous learning throughout the product lifecycle. Effective studies reveal the factors that have an influence on process variability. A well-conceived process simulation provides initial and periodic feedback on the state of control of the aseptic process. This information should translate to appropriate decisions throughout the product lifecycle, such as improvements in operational design and monitoring.

Outcome

The API and finished parenteral lots found to be non-sterile were rejected. Intensive aseptic activity by personnel was considered the route of contamination. After the repeated sterility failures, the finished prod-

uct manufacturer voluntarily recalled over 50 finished product lots due to concern that these lots were non-sterile. The sterile API firm ultimately modified the process to include semi-closed process concepts as well as automation.

Case Study 2: Assuring Container-Closure Integrity throughout Manufacture

Background

Distributed parenteral drug product was found to be contaminated with *Enterobacter cloacae*. Testing of previously unopened vials grew this microorganism and others, including *Xanthomonas maltophilia*.

CGMP Issues

Container-closure integrity problems were identified. A production operator dropped finished bulk pallets containing sealed glass vials that had already been through secondary packaging. When cleaning the spillage, production personnel also took the unusual step of washing the ostensibly still intact vials with potable water from a nearby sink.

Quality System Context

The *packaging and labeling system* was most deficient in this case. Poor handling of sealed glass vials at the final packaging stage was considered the root cause of the non-sterility. The rough handling of these bulk vials resulted in subvisible and hairline cracks in the vials. *Enterobacter cloacae* and other microorganisms apparently were introduced to the product when the firm performed the washdown of the glass vials with potable water. FDA collected several water samples at the firm and the same organism, *E. cloacae*, was isolated from the water hose and the sink.

A critical CGMP concept was reinforced in this case. While it is routinely stressed that careful controls are needed when the sterile product is exposed during processing, at the essence of CGMP is the principle that every production phase through to packaging must be robust. A firm's quality system should assure proper design, control, and maintenance of all facets of the manufacturing operation.

Outcome

The product was shipped and many Adverse Drug Events (ADEs) of septicemia were reported to FDA.

Cultures of previously unopened vials grew *E. cloacae*. Patient blood cultures yielded *E. cloacae*. It was determined that container-closure integrity of this parenteral product was lacking.

At least one lot was "directly implicated" in septicemia, and other lots were thought to possibly pose this hazard. Over 25 reports of septicemia were received by FDA naming the most worrisome lot or "unknown." The firm voluntarily conducted a Class 1 recall ("strong likelihood that product will cause serious adverse health consequences or death") of more than 10 lots manufactured during the period of concern.

Case Study 3: Modified 0.2-micron Filter Design and Change Control Systems

Background

A filter vendor changed the geometrical design of the outer cage of a 0.2-micron sterilizing-grade cartridge. The vendor considered the change to be a minor, aesthetic one that would not affect reliability or effectiveness of the filter.

CGMP Issues

The filter vendor issued a letter notifying customers of the filter design modification and stating that studies indicated that the change appeared to be only a minor one.

However, for their part, the sterile drug manufacturer's change control system was expected to assess whether the modified sterilizing-grade filter continued to be suitable for its intended use.

Quality System Context

The *facilities and equipment system* was most deficient in this case. The change control program within an effective quality system should accurately assess the potential for a problem due to an equipment modification and specify how the significance of the change is to be evaluated. If product-specific studies (5) had been conducted in this case, major product loss due to equipment failure could have been avoided.

Outcome

Several integrity failures (post-processing) followed, including some double failures of redundant filter con-

figurations. The vendor later recalled the filters. Although the vendor conducted some studies before releasing the new filters to the market, the studies did not detect an increased rigidity of the cage that afforded inadequate expansion room to accommodate filter medium swelling during some manufacturing operations. The lack of adequate expansion room resulted in the rupture of some filters during processing, depending on the liquid being filtered and the processing conditions.

Vendor claims and conclusions should be noted. An essential element in a firm's quality system, however, is a change control program to adequately assess whether equipment modifications will adversely affect their unique operation. Ultimately, in this case, the affected lots were rejected by the manufacturer, and the firm returned to using the original, suitable filter design.

Case Study 4: Blow-Fill-Seal (BFS) Equipment Design and Maintenance

Background

A firm experienced both sterility and media fill failures. *Stenotrophomonas maltophilia* was identified as a sterility failure isolate. Media fill isolates included *Pseudomonas* spp. and *Acinetobacter* spp. The blow-fill-seal (BFS) processing line had a good prior sterility history.

CGMP Issues

Mold plates used to form the primary product container were chilled with cooling water. This demineralized potable water was held in a tank at low temperature prior to use. When sampled, the cooling water yielded very high microbial counts. Leaks developed in the mold plates, allowing contaminated water to infiltrate into product, causing non-sterility.

Based on this significant breach in equipment integrity, among the most relevant CGMP deviations were the unsuitable processing equipment and the lack of an adequate preventative maintenance program.

Quality System Context

The *facilities and equipment system* was most deficient. The unsuitable equipment and inadequate pre-

ventative maintenance program were key factors in the product contamination.

Outcome

Both the sterility failure and media fill failure were attributed to contamination by cooling water. Pinhole leaks in the aseptic filling machine's mold plates allowed cooling water to directly contaminate the product. The exact date of problem occurrence was unknown, making the corrective and preventative action (CAPA) plan more difficult. Numerous lots were rejected. The firm concluded that frequent visual inspections of BFS molds for leaks had not provided for sufficient preventative maintenance, and it implemented corrective measures including regular testing of molding equipment pressure integrity.

Case Study 5: Parenteral-Grade Drug Substance Pyrogenicity

Background

An API manufacturer produced an active ingredient that was used to manufacture both injectable and tablet products. The API was tested against United States Pharmacopeia (USP) monograph requirements. It was produced by a multi-step process beginning with fermentation and ending with purification and isolation steps. Deionized water was used for cleaning equipment, a dissolution step, and as a washing solvent in the final processing steps, including final purification. Numerous adverse reactions (including serious pyrogenic reactions) occurred in patients taking parenteral products produced by two different dosage form manufacturers who used the supplier's API.

CGMP Issues

The FDA identified a number of CGMP problems during an international inspection of the API manufacturer. For example, the firm used unsuitable water in final processing steps. The firm lacked an adequate change control system. No validation was done when the firm scaled-up the process a few years earlier, although multiple significant changes to the process were implemented at that time. There also was no equipment usage log for a spray dryer (used for multiple products) that was used in the API process. The same person signed as operator and checker for a batch step in many instances.

Some of the firm's records were rewritten without explanation.

The possible contributors of endotoxins and any potential capability of the process to destroy or remove endotoxin had not been evaluated. The inspectional review of the process ultimately found that there was little or no opportunity for endotoxin reduction in the process.

The FDA inspection also found that the firm's composite testing of the finished API had revealed instances of batches approaching, as well as at, the endotoxin acceptance limit. Major laboratory controls deviations were found, including a failure of the microbiology laboratory to perform endotoxin controls required by the USP Bacterial Endotoxin Test. Water used for purification steps and final equipment rinses was not tested for total microbial counts. There was also no program to determine gram stain, or identity, of microorganisms. The audit of the chemistry laboratory found that impurity tests for the finished API were not validated and that the high performance liquid chromatography system suitability was only conducted monthly. Although the API firm received customer complaints from finished parenteral manufacturers reporting numerous occurrences of adverse reactions upon administration (infusion) of the firm's drug, the firm did not adequately identify the root cause of the product safety problem and repeatedly failed to implement an effective CAPA plan.

Quality System Context

With respect to the API vendor, multiple quality system elements were found to be highly objectionable, as detailed above.

In addition, while the API manufacturer's quality problems were clearly numerous, the *materials system* of the finished dosage form manufacturers also was in question. It is useful to think back in one's experience and consider how many times raw material variability has been the origin of a product problem that led to defects, product loss, rejections, or recalls. This writer has frequently seen inadequate raw materials named as the cause of product quality failures. In a CGMP-compliant quality system, the materials system should provide ongoing assurance of acceptable raw material quality. A different approach to incoming lot testing, or a qualification program that better gauged supplier reliability, might have prevented use of multiple lots of the low quality drug substance (23). For example,

conducting an effective audit of a vendor's facility is a dependable way to prevent a supplier from becoming the weak link in what might otherwise be a strong quality system.

Outcome/Discussion

In this case, there was a fundamental failure of the API firm to adequately consider intended use of the API when designing the process. The firm also sold the API for use in nonparenteral dosage forms. The firm used the same manufacturing approach when producing lots destined for parenteral dosage forms as that for oral solid dosage forms.

Overall, the API firm had very deficient CGMPs, including little assurance of process or laboratory control and unacceptable water systems and standards. The greatest amount of bacterial endotoxin was contributed during the final wash of crude active. Additional contribution of endotoxin might have occurred during other steps (e.g., cleaning), in which rinse water with significant endotoxin load was used to wash product contact surfaces. When the FDA tested individual samples from discrete parts of drums of a given batch, some of these samples failed USP Bacterial Endotoxin specifications. Pyrogen testing, performed as part of the joint FDA and Centers for Disease Control investigation, also yielded multiple pyrogenic results.

In line with the data seen throughout this case study, however, some of the other samples were non-pyrogenic. Due to the firm's lack of process control, there was significant potential for intra-batch variation (i.e., drum to drum variability). The firm's investigations had used composite samples. Medical practitioners reported over 200 ADEs following administration of the contaminated drug. Recalls and market withdrawals by both the API and finished product manufacturers followed, due to major quality and safety concerns.

The FDA placed the API firm on import detention. The firm remained in this status for multiple years due to failure to reach minimal compliance with CGMP. The firm ceased manufacturing the API that was associated with the ADEs. Several years later, under new ownership as well as new quality assurance managers, and after assistance of a consultant, the firm made numerous corrections and was allowed to resume shipping other APIs.

Case Study 6: Emergence of a Persistent and Problematic Environmental Contaminant

Background

A firm experienced multiple media fill failures on a specific line, with the same recurring fungal isolate common to each of them. While not in the same proportion or frequency as the fungal microbe, some additional microorganisms were also isolated.

Environmental monitoring data did not include any past isolations of this particular organism. Following the media fill failure, the investigation required environmental sampling at various new locations in the aseptic processing area.

CGMP Issues

The existing environmental monitoring systems did not recover this organism before the initial media fill failure. In addition, the environmental monitoring performed during the media fill failures did not exceed any alert or action levels. However, when the firm created an extensive environmental sampling plan as part of the investigation, it identified many instances of this microorganism on the aseptic processing equipment and in multiple locations in the room. The firm came to the conclusion that the organism was on the aseptic processing line and the problem was due to inadequate cleaning and sanitization. Among the concerns was an area inside a machine panel, located in the critical zone, that had never been cleaned or sampled. Following the investigation, the machine panel was considered a primary source of the spread of contamination in the class 100 (ISO 5) area and aseptic processing room.

Quality System Context

While the facilities and equipment system was clearly substandard in this case, equally notable was the deficient *laboratory system*. The environmental monitoring program was inadequate, as it did not detect a very significant drift in environmental control. As a result, it could not provide the early warning needed to prevent product contamination. The investigation traced media fill contamination to the failure to adequately clean and disinfect the aseptic filling line (i.e., although product contact parts were sterilized, other parts of the line and room posed contamination risks).

Outcome

The firm fumigated the room to try to control the contamination. However, the firm later reported to the FDA that another media fill failure had occurred with the same fungus present. The firm concluded that more work had to be done to remedy the root cause and then they would again attempt to perform three successful media fills to confirm the return to a state of control. After further intensive efforts, the firm restored appropriate conditions for the aseptic production of a sterile drug. This case study is consistent with what is seen in many cases: once such a contaminant becomes airborne and is allowed to proliferate unchecked, it is not a simple task to bring the environment back under control.

Case Study 7: Extensive Aseptic Interventions by Personnel

Background

Approximately 60% of the units run in a media fill were found to be microbiologically contaminated. The firm implemented minor corrections to their satisfaction. The firm then ran three further media fills. A second media fill yielded a high level of contamination. Isolates in both failures were common skin-borne microbes (e.g., *Staphylococcus* spp.). A sterility failure had also occurred in the prior 6 months.

CGMP Issues

Multiple significant aseptic maneuvers were required by this small-volume parenteral process. Media fill investigations indicated that these steps appeared to pose significant risk to the product. Aseptic gowning by personnel was inadequate.

Quality System Context

The *production system* was most deficient in this case. Specific problematic aspects of this system were personnel training (24), supervisory oversight of operations, appropriate aseptic gowning, and adequacy of the process design.

Outcome

The firm felt that the initial media fill failure was likely an anomalous episode that could be prevented by implementing some minor corrections. Neverthe-

Table I
Results of Three Additional Media Fills

Lot	Media Fill Batch Result
1	No contamination
2	Over 95% contaminated
3	No contamination

less, as per the firm's investigation (and company standard operating procedure), the firm required three successful lots to ensure that the line had returned to a state of control following the corrections. The three additional media fill lots yielded the results in Table I.

It is noteworthy that if only one media fill batch had been run in this situation, the firm could have returned to production/release of commercial lots without the knowledge that a non-sterility problem still existed. Further, because the firm's well-conceived media fill program afforded an accurate simulation of the risks associated with various aseptic manipulations, it ultimately helped diagnose a major problem.

The cause was considered to be personnel's performance of aseptic connections and manipulation at the bulk stage under Class 100 (ISO 5) unidirectional flow. The investigation indicated that personnel introduced the contamination in the course of a difficult (and routine) aseptic manipulation of sterile equipment prior to the filling stage of the process. The firm concluded that the microorganisms then multiplied while staged in bulk for several hours prior to filling. A very significant aspect of this contamination problem was the fact that there was a design flaw in the gown routinely donned by personnel and asepsis was compromised. The firm corrected the gowning deficiencies and the equipment connection is now sterilized-in-place (SIP).

Case Study 8: Migration of Contamination Liberated during Facility Construction

Background

A firm undertook major construction in a cleanroom next to the personnel entry airlock (e.g., gowning area). The construction occurred over a one-month period and coincided with continued production. Following an initial media fill failure, the firm's investigation concluded that practices unrelated to the con-

struction were the likely sources of the non-sterile units. The firm corrected the apparent root causes. A repeat media fill was then performed. A second media fill failure occurred. A second thorough investigation by the firm concluded that the contaminants in the media fill vials had migrated from the area of the construction activity. Sporeforming bacteria (*Bacillus*, sp.) were identified as isolates in both media fills.

CGMP Issues

The firm did not adequately assess the risk posed by construction activities.

Quality System Context

The *production system* was most deficient in this case. It is essential that any change in normal, qualified conditions be carefully evaluated by production and quality management (Fig. 1).

FDA has seen this scenario with surprising frequency: a firm performs construction in an area that is considerably removed (in some cases, several rooms away) from the aseptic processing room and presumes that the construction will not affect the sterility assurance of the product. Unfortunately, it is not uncommon for the contamination to ultimately migrate to the aseptic processing room and into the product. Many sterility failures and media fill failures have been attributed to contamination from nearby construction. For example, moving of walls is a common culprit in the liberation of sporeformers (most commonly fungi) into the cleanroom environment. These experiences should caution a firm to assess the potential impact of such deviations from normal conditions. Deviation and/or change control systems provide a formal mechanism for evaluating these issues.

Written procedures should address returning a facility to normal operating conditions when construction or other activities (e.g., maintenance) are considered to have a potentially adverse impact. In these cases, a firm should either elect not to produce product for a specific period or, where appropriate, implement special precautions and increase monitoring to detect any drift in environmental control.

Outcome

Multiple lots were found to lack assurance of sterility and those already distributed were recalled. The firm

temporarily suspended operations. The firm ultimately restored adequate conditions and resumed aseptic processing following successful media fill requalification.

Conclusion

The case studies described in this paper illustrate how sterile dosage form contamination issues can emerge where deficient design concepts or operational practices exist. These case studies generally include older approaches to the design, control, or maintenance of an aseptic manufacturing operation. In recent years, it is quite rare to see a firm constructing a new line using antiquated design concepts. The aseptic processing industry has been largely engaged in the modernization of processes and systems over the last decade (25). The trend toward modern design concepts includes a general movement toward closed and semi-closed systems and away from personnel-intensive aseptic processing. The marked increase in use of isolators and restricted access barriers, as well as the replacement of aseptic equipment assembly with SIP technology indicates increased attention to sterile product protection in the industry (26–29). As part of the Pharmaceutical CGMPs for the 21st Century initiative, the FDA has made it clear that such modern approaches (30) for improving product quality are welcome (31, 32). This openness is reflected in the recently issued Guidance on Sterile Drug Products Produced by Aseptic Processing (September 2004), which emphasizes designing quality into aseptic processing operations through the use of current science and technology (1).

The daily operations of the pharmaceutical industry determine safety and efficacy of drug products. Industry managers are responsible for implementing robust systems that support sustainable CGMP compliance. Sustainable compliance is fundamentally founded in well-conceived operational design. Management oversight (e.g., CAPA, change control, process trending, maintenance, ongoing supplier scrutiny) of operations and support for continuous improvement is at the core of maintaining a consistent process and preventing product defects (33, 34). Training is an integral part of assuring these basic quality system objectives are met and it is hoped that the case studies in this paper might be helpful as a practical CGMP training tool for aseptic production facilities. With sound design and a responsive quality system, the industry will continue to reproducibly manufacture high quality sterile drugs by aseptic processing.

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References

1. US Food & Drug Administration. *Guidance on Sterile Drug Products Produced by Aseptic Processing*, September, 2004.
2. Annex 1, Manufacture of Sterile Medicinal Products, European Union GMPs, European Commission, 2003.
3. Block, S. S. *Disinfection, Sterilization, and Preservation*, 5th Edition. Lippincott, Williams and Wilkins: Philadelphia, PA, 2000.
4. Parenteral Drug Association. *Process Simulation Testing for Aseptically Filled Products*; Technical Report No. 22, 1996.
5. Parenteral Drug Association. *Sterilizing Filtration of Liquids*; Technical Report No. 26., 1998.
6. Ljungqvist, B.; Reinmuller, B. *Clean Room Design: Minimizing Contamination Through Proper Design*. Interpharm Press: Buffalo Grove, IL, 1997.
7. Oji, R. T. Regulatory aspects concerning the quality controls of microbiological and non-viable particulate contamination in pharmaceutical manufacturing. *American Pharmaceutical Review* **2004**, 7(1), 18-22, 68.
8. Matthews, Brian R. *The Davonport Incident, the Clothier Report, and Related Matters—30 Years On*. *PDA Journal of Pharmaceutical Science & Technology*. **2002**, 56 (3), 137-149
9. Avallone, H. Current regulatory issues regarding parenteral inspections. *Journal of Parenteral Science and Technology* **1989**, 43(1), 3-7
10. "Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation," Final Rule 21 CFR 200.51, Federal Register May 26, 2000 65 (FR 34082).
11. FDA Recalls and Safety Alerts, <http://www.fda.gov/opacom/7/alerts.html>

12. Snyder J. E. Corrective and preventive action planning to achieve sustainable GMP compliance. *Journal of GXP Compliance* **2002**, 6(3), 29-39.
13. Baseline Pharmaceutical Engineering Guide for Sterile Manufacturing Facilities, *International Society for Pharmaceutical Engineering* **1999**, 3 (January)
14. Friedman, R.; Mahoney, S. Risk factors in aseptic processing. *American Pharmaceutical Review* **2003**, 6(1), page 44-46, 92.
15. Massa, T. Life Cycle Management for Process and System Control: An Industry Proposal. Manufacturing Subcommittee, Advisory Committee for Pharmaceutical Science. July 20, 2004.
16. 21 CFR 210 and 211, US Food & Drug Administration, US Printing Office.
17. Food & Drug Administration. Compliance Program Guidance Manual – Drug Manufacturing Inspections, CPGM 7356.002, February 2002.
18. Famulare, J. Quality Systems Guidance. PDA/FDA Joint Regulatory Conference, Washington, DC, September 2004.
19. US Food & Drug Administration. Draft Guidance on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. September 2004.
20. Friedman, R. Routes of contamination: aseptic processing case studies. *European Journal of Parenteral & Pharmaceutical Sciences* **2005**, 10(1), 3-7.
21. Goode, R.; Evans, K. The scientific method: application to FDA regulated industry. Part I of III. *Journal of Validation Technology* **2003**, 10(1), 37-43.
22. US Food & Drug Administration. Sec. 490.100, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08), March, 2004.
23. Cooper, J.; Bruegger, P.; Fanning, M.; Matsuura, S.; Poole, S. "Alert and Action Endotoxin Levels for APIs: A Collaborative Study." Parenteral Drug Association Annual Meeting, December 2002.
24. Vesper, J. L. Chapter 19. Training and Learning: Critical Contributors to Quality. In *Pharmaceutical Quality*; Prince, R., Ed.; DHI Publishing: River Grove, IL, 2004.
25. FDA Advisory Committee for Pharmaceutical Science, October 22, 2002.
26. Lysford, J.; Porter, M. Barrier Isolation History and Trends. International Society for Pharmaceutical Engineering Washington Conference: Barrier Isolation Technology, June 2004.
27. Farquharson, G. Cleanrooms and associated controlled environments. Part 7: Separative Devices. 8th Pharmaceutical Isolator Conference, Warwick, U.K., December 2004.
28. Wood, R. T. Sterilization of API manufacturing equipment. *PDA Journal of Pharmaceutical Science & Technology* **1999**, 53(5), 231-234
29. Sinclair, C. S.; Tallentire, A. Performance of blow/fill/seal equipment under controlled airborne microbial challenges. *PDA Journal of Pharmaceutical Science & Technology* **1995**, 49(6), 294-299.
30. Khorzad, D.; Khorzad, A.; Herche, J.; Reich, M.; Caputo, R. Design and operational qualification of a vapor-phase hydrogen peroxide biological indicator evaluator resistometer (BIER) unit. *Pharmaceutical Technology* **2003**, 84-90
31. Woodcock, J. The concept of pharmaceutical quality. *American Pharmaceutical Review* **2004**, 7(6), 10-15.
32. Food & Drug Administration. Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach, Final Report, September 2004.
33. Friedman, R. Chapter 3: Quality Management in the American Pharmaceutical Industry. In *Pharmaceutical Quality*; Prince, R., Ed.; DHI Publishing: River Grove, IL, 2004.
34. Dwyer, T.; Keresty, G.; Sherry, B. "The cost of non-conformance: the linkage between quality performance and business results. *Pharmaceutical Engineering* **2001**, 20(5), 8-14.